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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,399	08/26/2003	Ben-Zion Dolitzky	1662/60903	6089

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,399	DOLITZKY ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *11-17,20-29,32-34,36,41,42,44 and 47-51* is/are allowed.

6)☒ Claim(s) *1-3,5-10,18,19,31,35,37-40,43,45 and 46* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/17/2006 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Harnden 1990, with Harnden 1989 supplemental.

In Harnden 1990, see the preparation in the first full paragraph on page 501. The crystallization is done from water. The claims recite among others, methanol/water. However, no limits are set on the ratio of the two solvents; the claim would read on e.g. one part per billion of methanol in water. However, tiny traces of methanol would be expected to be present, because the starting material was prepared in methanol. Footnote 8 is Harnden 1989, and as seen in the last paragraph of page 1741, the starting material was made in methanol.

The traverse is unpersuasive. Applicants first argue that this is not an anticipation, that it is really Harnden 1990 in view of Harnden 1989. This is not agreed with. Harnden 1990 anticipates; it teaches the claims process. Harnden 1989 is a supplemental reference shoes sole purpose to show what one of ordinary skill in the art would be expected to know, viz., that the starting material was made in methanol. This is entirely proper. A reference is considered to anticipate if its teachings plus what the skilled artisan is expected to know would yield the invention claimed, *In re Graves*, 36 USPQ 2nd 1697, 1701.

Second, applicants argue as follows: "One skilled in the art reading Harnden 1990 would not necessarily know how the crude famciclovir of Harnden 1989 was prepared. The crude famciclovir of Harnden 1989 is also not inherently disclosed in Harnden 1990 because the crude famciclovir as prepared by the process disclosed in Harnden 1989 does not naturally flow from the disclosure in Harnden 1990."

This argument is entirely mistaken. The Harnden 1990 sentence which sets forth the preparation of Famciclovir is footnoted by footnote 8, which is Harnden 1989. This conveys to one of ordinary skill in the art that the procedure of Harnden 199 was used in the reference Harnden 1990. If applicants do not agree with that sentence, when what does footnote 8 convey?

Next applicants say that reference does not "explain the meaning of a term used in Harnden 1990." This is not agreed with. It is there to set forth the meaning of footnote 8. The Harnden 1989 reference is footnote 8, and therefore the actual reference Harnden 1989 is evidence of what the footnote 8 was intended to convey.

Next applicants argue: "Examiner misinterpreted the disclosures of Hamden 1989. The Examiner asserted that Hamden 1989 teaches famciclovir containing traces of

methanol. Applicants respectfully disagree." That is not what the examiner asserts for the reference. The examiner says that the reference teaches "the starting material was made in methanol." . The examiner concludes that tiny traces of methanol would be expected to be present, because the starting material was prepared in methanol.

Applicants then discuss the chloroform extraction. First, the chloroform extraction is of limited significance, since chloroform is miscible with methanol, and hence the chloroform extraction would bring with it some of the methanol. Second, the solvent removals cannot be exhaustive since it is already known that these compounds form solvates with methanol. Claim 35 does not set any minimum amount. Even the most tiny trace is enough to qualify (see SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398 (CAFC 2005)), and applicants cannot argue that there was absolutely no methanol left at all.

To rebut this, applicants have cited the Wikipedia reference on Solvent, point to the "like dissolves like" and then contends that "chloroform would not be expected to bring with it methanol". Applicants are reading far too much into this rule of thumb. The numbers 4.8 and 33 are not that far off, and applicants are entirely mistaken. One of ordinary skill in the art knows that chloroform is miscible with pretty much all conventional organic solvents. At any rate, to rebut this line of reasoning, the reference Solvent miscibility Table <http://www.phenomenex.com/phen/Doc/z366.pdf> shows that the two solvents are miscible. In addition US 20050007430 A1 is cited for the statement in paragraph 0019 "Methanol and ethanol are miscible with chloroform in all proportions". Therefore, the chloroform will indeed bring with it all the methanol.

Next, applicants argue that step g would remove methanol. However, as noted above, Second, the solvent removals cannot be exhaustive since it is already known that these compounds form solvates with methanol. Applicants are reminded that in their example 7, the methanol was retained even though the material was heated for 65°C for 2 hours in a vacuum! This is probably much more drastic than what Harnden 1989 did, since "solvent removal" does not normally involve such drastic conditions. Therefore the statement that the methanol would be removed is refuted by applicants own specification.

Claims 1-3, 5-10, 18-19, 31, 37-40, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by with Harnden 1989; US 5017701, US 5066805; US 5138057, US 6846927, 6342603, Freerer, 6437125, and WO 200006573.

In Harnden 1989, note the crystallization of (14) from Ethyl acetate/hexane. In US 5017701, note column 7, line 31, where it is crystallized from hot n-butanol; the same is seen in example II-5 of 6342603. In US 5066805, see Column 3, where the solid appears to be prepared by evaporation from a chloroform/methanol solution. In US 5138057, see Column 8, lines 11-12 and 33, where it was crystallized from Ethyl acetate/diethyl ether and from n-butanol. In 6846927, the product was recrystallized from n-butanol but then reslurried in n-heptane, stirred and filtered, i.e. triturated with n-heptane. In Freerer, the crystallization was done from hot isopropanol; see last example. A similar procedure was done with in example 9 of 6437125. In WO 200006573, see synthesis example 11, which has trituration with diethyl ether. In Brand, see page 5251, with crystallizing from aqueous acetone.

Insofar as Claim 31 is concerned, the references which recited n-butanol anticipate, and provide further evidence that this is Form II, since the same method is used. Insofar

as Claim 18 is concerned, the reference which recites diethyl ether trituration anticipates, and provide further evidence that this is Form I, since the same method is used. Insofar as Claim 30 is concerned, the references which recite isopropanol anticipate, and provide further evidence that this is Form I, since the same method is used.

The traverse is unpersuasive. MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the particular crystalline form. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the crystalline form.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is.

The only difference is a characteristic about which the reference happens to be silent. See also Ex parte Anderson, 21 USPQ 2nd 1241 at 1251, discussion of Rejection E. There, the decision states, "There is ample precedent for shifting the burden to an applicant to reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253). The "properties" branch of that statement applies here.

It is well settled that the PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical. An applicant's burden under these circumstances was described in *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, or 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products (footnote omitted).

Applicants argued in their response of 2/28/2006 (now incorporated into the recent response) that the solvent was different. Thus, for example, Harnden (1989) uses ethyl acetate/hexane, whereas applicants use ethyl acetate alone or ethyl acetate/toluene. First, the examiner must point out that toluene and hexane are rather similar solvents, as both are hydrocarbons. But more importantly, applicants reasoning seems to be that only ethyl acetate alone or ethyl acetate/toluene will produce form I, and that if one does not use ethyl acetate alone or ethyl acetate/toluene, one does not get Form I. Applicants present no

evidence that this is actually true. The specification makes no such assertion. The same is true for the assertion that Form II is made from ethanol or n-butanol. Actually, the specification teaches that quite an assortment of other solvents will make these forms, including IPA, THF, methylene dichloride, acetonitrile, diethyl ether/ methylene dichloride, dimethylacetamide, acetone, acetonitrile/toluene, methylene dichloride/toluene and chloroform. Therefore, any reasoning that the method is different and therefore the product is not there is not accepted. Applicants are also sometimes drawing very fine distinctions. Thus, for example, at one point applicants state that "Trituration is defined as mixing a solid powder with a solvent, and is different from washing a solid collected on a filter paper with a solvent." This hardly seems any difference at all. If the solid collected was a powder -- which is a fairly broad term – then the prior art process falls within "trituration", since "mixing" is certainly broad enough to cover washing.

If this reasoning were accepted, applicants could patent an old compound simply by making it in a new manner and supplying some characteristic that the prior art didn't happen to mention, such as density (e.g. "density is not 1.4"), melting point, "refractive index of 2.0", solubility in some obscure solvent, spectroscopic data, and then simply point to the silence of the reference, as applicants have done here. Or one could add properties like or "does not explode on tapping" or "in the form of microneedles" or, as here, give the XRD data. It is always possible to add some such property, so this amounts to saying that an old compound can be patented just by making it in a slightly different manner. There is no support for this in law.

Applicants now argue, "Applicants note that the crystalline form is not a "property" of famciclovir. Crystalline famciclovir Form I and Form II are two novel forms of

famciclovir. Thus, crystalline famciclovir Form I and Form II are not properties of an old compound." This cannot possibly be agreed with. The physical form that a compound takes is of course a "property". A physical property is not the same thing as an e.g. biological property, but a physical form is still a property, and indeed, being polymorphic is also a property. Are applicants seriously arguing that X-ray diffraction peaks for example are not a property? At any rate the reference "Chemistry Research Guide - Physical & Chemical Properties" is cited, which says, "CRC Handbook of Chemistry and Physics. 84th ed. (Annual) Premier source for property data. Provides information (in tabular format) for organic and inorganic compounds and the elements. Property data includes molecular weight (mw), physical form ...." This demonstrates that, as the word is commonly used, property of a chemical compound includes physical form.

In the paragraph bridging pages 13-14, applicants discuss claim 18, but the relevant reference is WO 200006573.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The intention of claim 5 is unclear. The claim limitation in the claim now is already required by claim 1, according to the amended claim limitation.

The examiner is at a loss to understand the traverse, and it may be that the claim language does not reflect applicants' intentions. Claim 1 already requires that all other forms, including form II, total less than 5%. Since all forms combined must sum to less than 5%, the Form II must of necessity be less than 5%, which is all that claim 5 requires. If applicants disagree, they are invited to describe a material which falls within claim 1 but does not fall within claim 5. It may be that applicants intend "another Famciclovir crystalline form" to mean "each individual form", but that is not what the claim says. In other words, if a specimen actually had 4% Form II, 4% Form III and 4% Form IV, that would be thought of, and properly described as having 88% Form I, and 12% of "another Famciclovir crystalline form" since all of II, III and IV would be another form, and therefore would not fall within claim 1. In other words, the phase "another Famciclovir crystalline form" is a collective term denoting all forms which are not form I.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DMF/water, does not reasonably provide enablement for all other choices. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Brand teaches that the use of aqueous acetone gives famciclovir, not famciclovir hydrate. This then casts doubt on other aqueous solvents except for the aqueous DMF in the example.

The traverse is unpersuasive. It is correct that Brand teaches that aqueous acetone gives famciclovir, but does not explicitly state that the product was Famciclovir and not famciclovir hydrate.

The examiner does not need rigorous proof. All that is needed is a reasonable basis to doubt. MPEP 2164.05 states, "Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary" that the claims are indeed enabled.

In response, applicants make two arguments. First, they state: "Especially because Brand used only ^{1}H-NMR and ^{13}C-NMR performed in solution, the NMR techniques used by Brand would not be expected to differentiate famciclovir from Famciclovir monohydrate."

This is simply untrue. First, Brand used elemental analysis to characterize the material, and all elements C, N and H were within proper error limits of the calculated for the non-hydrate. If this were actually the monohydrate, all three elements analysis would be outside the normal error ranges for the calculated percentage. Second, their reported melting point of 103-105°C is virtually identical, as noted by Brand, to the literature value of 102-103°C. By contrast, Harnden 1990 reports 87-95°C for the monohydrate.

Applicants second argument is: "One skilled in the art would recognize that one may need to use ^{13}C-solid-state NMR, preferably coupled with the use of high power proton decoupling, magic angle spinning and cross-polarization, to differentiate a crystalline substance from its hydrate." No evidence whatsoever is presented that such techniques are needed. Harnden 1990 as well as EP 885223 both report the monohydrate without resort to such techniques.

Thus, the reference says that it is Famciclovir, and it has the correct elemental analysis for Famciclovir, and it has the melting point for Famciclovir, and not the melting point for Famciclovir monohydrate, and hence there is every reason to assume that the reference has exactly what it says it has.

Claims 45-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Where is this in the specification? The specification says that it can make Famciclovir itself of this level of purity, but nowhere does it say that the methanol or ethanol solvates have this level of purity.

Claim Objections

Claims 30 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

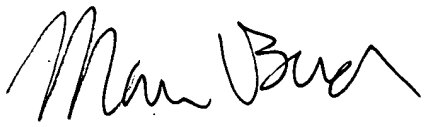
All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Mark L. Berch
Primary Examiner
Art Unit 1624

11/22/06